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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/726,211	10/04/96	TORMO M	UTXC:504

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MARK B WILSON
ARNOLD WHITE & DURKEE
P O BOX 4433
HOUSTON TX 77210-4433

EXAMINER	
SCHWARTZMAN, R	
ART UNIT	**PAPER NUMBER**
1636	21

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/726,211	Tormo et al.
Examiner	**Group Art Unit**
Robert Schwartzman	1636

☒ Responsive to communication(s) filed on *Jun 8, 1999* .

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-41, 43-50, and 52-56* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-41, 43-50, and 52-56* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

This Office action is in response to the amendment filed June 8, 1999. Claims 42 and 51 have been canceled and new claim 56 has been added. Claims 1-41, 43-50 and 52-56 are pending in this application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5-9, 31, 33-42 and 47-55 remain rejected and new claim 56 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is maintained for the reasons of record in the previous Office action mailed January 4, 1999.

Claims 1-3, 5-9, 31, 33-42 and 47-55 as amended are drawn to a composition comprising an antisense oligonucleotide comprising at least 8 nucleotides of SEQ ID NO:1, the 18-mer which has been disclosed to be effective in reducing the expression of the Bcl-2 gene in a cell and inhibit cell proliferation. The new wording reads on an oligonucleotide comprising any 8 nucleotides from SEQ ID NO:1 in any order, effectively encompassing any possible sequence and targeted to any region of Bcl-2. Therefore, the amendment does not add any limitation which overcomes the outstanding written description rejection. It is suggested that amendment of the claims to be drawn to an oligonucleotide comprising at least 8 contiguous nucleotides of SEQ ID NO:1 and which is targeted to the translation initiation site of Bcl-2 mRNA may obviate the rejection. New claim 56 is limited to 8 consecutive nucleotides of SEQ ID NO:1. This claim still does not sufficiently overcome the written description rejection as the oligonucleotide still may be targeted to any region of Bcl-2 as it is open to any sequence in addition to the 8 consecutive nucleotides. It is suggested that the claim be further limited to an oligonucleotide which is targeted to the translation initiation site of Bcl-2 mRNA.

Applicants argue that the specification provides ample written description for the structural characteristics and properties of the claimed invention through the description of SEQ ID NO:1, complementary oligonucleotides that bind the Bcl-2 gene, the size range that may be used, an example of an oligonucleotide that is not completely complementary but still may be used and two contrasting oligonucleotides that are not complementary and are not effective. This

argument has been fully considered but is not deemed to be persuasive. As discussed above, the claim amendments do not restrict the claimed oligonucleotide in any way regarding sequence or target site. Therefore, the structural characteristics and properties of the claimed invention have not been adequately described in the specification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-9, 31-37, 39-41, 48-50 and 52-54 remain rejected and new claim 56 is rejected under 35 U.S.C. 103(a) as being unpatentable over Evan or Reed or Green *et al.* in view of Tari *et al.* This rejection is maintained for the reasons of record in the previous Office action mailed January 4, 1999.

To summarize the rejection, Evan, Reed and Green *et al.* each teach antisense oligonucleotides targeted to Bcl-2. The oligonucleotide preferably is targeted to the translation initiation site of Bcl-2. The antisense oligonucleotide or an expression construct encoding the

antisense oligonucleotide can be delivered into a cell as a liposome composition. Evan, Reed and Green *et al.* do not teach liposomes composed of neutral phospholipids. Tari *et al.* teaches compositions comprising an antisense oligonucleotide encapsulated in a liposome made from neutral phospholipids such as dioleoylphosphatidylcholine. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the present invention was made to make a composition comprising an antisense oligonucleotide targeted to Bcl-2 encapsulated in a liposome as taught by Evan or Reed or Green *et al.* and to use the liposomal formulations taught by Tari *et al.*, motivated by the teaching of Tari *et al.* that liposomes comprising dioleoylphosphatidylcholine impart improved stability and cellular uptake to the antisense oligonucleotides.

Applicants argue that the Office has mischaracterized Tari *et al.* and that Tari *et al.* does not provide guidance to specifically select a neutral lipid. Tari *et al.* teaches that the desirable properties are common to all liposome constructs. The broad teaching of the general advantages of a phospholipid liposome and an antisense methyl phosphonate oligonucleotide is not a teaching, suggestion or guidance of the neutral lipid and antisense Bcl-2 oligonucleotide composition of the present invention. Tari *et al.* discloses (column 6, Table 4) that the charged lipid dioleoylphosphatidylserine (DOPS) incorporates oligonucleotides with an efficiency greater than or equal to the compositions comprising neutral phospholipids, demonstrating that both neutral and charged lipids incorporate oligonucleotides and that the tested charged lipid does so better than most of the uncharged lipids tested, including dioleoylphosphatidylcholine (DOPC).

Applicants submit that this teaching may indicate that charged lipid constructs may be more therapeutically effective than uncharged liposome constructs, as a charged liposome contains as much or more oligonucleotides as uncharged lipids. The teachings of Tari *et al.*, including the teachings of the benefits of a charged lipid, must be considered as a whole in the obviousness of the claim invention. Applicants submit that there is a difference in the motivation for selecting a type of lipid that has a property of ease of handling in an experimental setting and that motivation for selecting the type of lipid that has a property of high uptake of oligonucleotides. Because the present invention relates to therapeutic applications, the uptake of oligonucleotides is the more desirable property, and is the property possessed by the charged lipid more so than the majority of uncharged lipids. Also, Tari *et al.* does not indicate that charged lipids are not easy to handle, only that neutral lipids do have this property. Thus, Tari *et al.* does not provide motivation for specifically selecting uncharged lipids from the teaching of charged and uncharged lipids.

This argument has been fully considered but is not deemed to be persuasive. Tari *et al.*, in the general disclosure of the patented invention, states that the preferred lipids are selected from phosphatidylcholines (neutral lipids) and phosphatidylserines (charged lipids) with DOPC (a neutral lipid) being a particularly preferred lipid (column 2, lines 10-14). Tari *et al.* could not more explicitly state that the neutral lipid DOPC is preferred over phosphatidylserines. Applicants' statements that DOPS is more effective than DOPC in incorporating oligonucleotides into liposomes is not agreed with. Table 4 in column 6 discloses that DOPC had an incorporation

efficiency of 92.5% ± 2.5% while DOPS had an incorporation efficiency of 95.0% ± 2.0%. One of ordinary skill in the art would consider these results to be statistically equivalent, especially when based on the results of only two experiments. Thus, there is no advantage taught for DOPS over DOPC. Furthermore, assuming *in arguendo* that the difference in incorporation efficiency between DOPC and DOPS was significant, one of ordinary skill in the art reading Table 4 would select dimyristoylphosphatidylcholine as the lipid of choice as it has the highest incorporation efficiency (97.5% ± 2.5%). Thus, a neutral lipid would be selected. In the face of the disclosure of Table 4, the statement in Tari *et al.* that DOPC was one of the easiest lipids to handle would be sufficient for the unbiased artisan to select DOPC from those lipids shown to have the highest incorporation efficiency for use in an oligonucleotide/liposome composition. Furthermore, DOPC was the only lipid shown to effectively deliver oligonucleotides to a cell. Given that there is no significant difference in oligonucleotide uptake between the different tested lipids there is no motivation in Tari *et al.* to use the charged lipid rather than DOPC in a composition. In fact, the disclosure of Tari *et al.* that DOPC is the preferred embodiment and that DOPC is one of the easiest lipids to handle, the showing that DOPC is effective for delivering oligonucleotides to cells and the absence of any showing using a charged lipid for oligonucleotide delivery and the teaching that their invention is designed for therapeutic applications, provides more than sufficient motivation to select DOPC for use in an oligonucleotide/lipid composition.

Applicants further argue that the previously submitted declaration of Drs. Tari and Lopez-Berestein was not properly considered by the Office. The declaration demonstrates the surprising and unexpected properties of the claimed invention over the teachings of the cited references and should be given substantive weight. The previous action's argument that liposomes comprising charged lipids are toxic to cells is inconsequential as Tari *et al.* already teaches that neutral lipids are preferred is an improper dismissal or the evidence presented by the applicants of the surprising properties of the claimed invention. Tari *et al.* teaches an enhanced specific therapeutic effect of the antisense oligonucleotides of its invention, which includes both charged and uncharged liposomal constructs. The data presented in the declaration demonstrates that charged liposomes are non-specifically toxic to the tested cell lines. This data is surprising and unexpected because it demonstrates the advantage of the presently claimed invention over the charged and uncharged liposomes taught in Tari *et al.*

This argument has been fully considered but is not deemed to be persuasive. As discussed above, a fair reading Tari *et al.* by one of ordinary skill in the art would not lead to the conclusion that charged lipids are better than, or even equal to, neutral lipids. This is based on the fact that Tari *et al.* states that DOPC is the most preferred embodiment, that DOPC is one of the easiest lipids to handle and that DOPC was used in all of the disclosed experiments except for the one in which different lipids were tested for incorporation efficiency. Since DOPC was the only lipid demonstrated to be effective in delivering an oligonucleotide to a cell one of ordinary skill in the

art would clearly expect DOPC to be effective in delivering oligonucleotides to a cell. Since Tari *et al.* did not test the effect of DOPS-based liposomes on cells the artisan could not draw any conclusions as to the effectiveness of such liposomes in delivering oligonucleotides to cells. The showing in the declaration of Drs. Tari and Lopez-Berestein of the effectiveness and lack of toxicity of liposomes containing DOPC cannot be considered to be surprising in view of Tari *et al.* as Tari *et al.* showed that DOPC-based liposomes were effective and non-toxic. The showing in the declaration that liposomes comprising 30% positively- or negatively-charged lipids cannot be said to be surprising in view of Tari *et al.* as Tari *et al.* never tested the liposomes containing DOPS for their effect on cells. Additionally, Tari *et al.* never teaches or suggests liposomes comprising 30% DOPS or any other charged lipid. Therefore, no comparison can be made between the results shown on the declaration and the teachings of Tari *et al.* Finally, even if a showing that charged lipids work less well than expected was surprising in view of the teachings of Tari *et al.*, this would only demonstrate an unexpected disadvantage of what is not being presently claimed, not an unexpected advantage of what is being presently claimed.

Claims 1-8, 10-36, 39, 44, 46, 48-50 and 52-54 remain rejected and new claim 56 is rejected under 35 U.S.C. 103(a) as being unpatentable over Abubakr *et al.*, Pocock *et al.* and Cotter *et al.* in view of Tari *et al.* and further in view of Evan. This rejection is maintained for the reasons of record in the previous Office action mailed January 4, 1999.

To summarize the rejection, Abubakr *et al.*, Pocock *et al.*, and Cotter *et al.*, taken together, clearly show that treatment of lymphoma cells having a t(14:18) translocation with an antisense oligonucleotide targeted to the translation initiation site of the Bcl-2 gene, either before or after administration to SCID mice, results in the inhibition of proliferation of the lymphoma cells and the prevention of lymphoma development in the mice. None of these references teach administration of the antisense oligonucleotide as a composition comprising neutral lipids. Tari *et al.* teaches compositions comprising an antisense oligonucleotide encapsulated in a liposome made from neutral phospholipids such as DOPC. Tari *et al.* teaches the benefit of using liposomes consisting of neutral lipids for the delivery of antisense oligonucleotides, including improved stability of the antisense oligonucleotide compositions under biologic conditions, improved uptake of the composition in cells, improved incorporation efficiency of the oligonucleotides into liposomes and enhanced specific therapeutic effect of the antisense oligonucleotides (column 2, lines 49-56). Evan *et al.* teaches the use of an antisense oligonucleotide targeted to Bcl-2 to prevent expression of the Bcl-2 protein (page 7, lines 10-29). The oligonucleotide preferably comprises the sequence of claimed SEQ ID NO:1 (page 15, lines 16-23). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the present invention was made to use an antisense oligonucleotide targeted to Bcl-2 to inhibit the proliferation of cells having a t(14:18) translocation resulting in overexpression of Bcl-2 as taught by Abubakr *et al.*, Pocock *et al.* and Cotter *et al.* and to administer the antisense oligonucleotide as a composition comprising a neutral phospholipid as taught by Tari *et al.*, motivated by the

teaching of Tari *et al.* that the neutral lipid composition imparts several benefits on the administration of an antisense oligonucleotide. It further would have been obvious to inhibit the proliferation of a lymphoma cell in a human as effects seen in immunocompromised mouse models of lymphoma and leukemia are recognized in the art to be reasonably predictive of results in humans. In terms of particular volumes, dosages and schedules of administration, one of ordinary skill in the art could practice routine optimization to determine appropriate volumes, dosages and schedules such as those that are claimed when converting treatments developed for mice into equivalent treatments for humans. It would further have been *prima facie* obvious to one of ordinary skill in the art at the time the present invention was made to make and use an antisense oligonucleotide targeted to the translation initiation site of Bcl-2 as taught by Abubakr *et al.*, Pocock *et al.*, Cotter *et al.* and Tari *et al.* and to have the oligonucleotide comprise the sequence of SEQ ID NO:1 as taught by Evan as Abubakr *et al.*, Pocock *et al.*, Cotter *et al.* and Evan each teach the targeting of the antisense oligonucleotide to a region comprising the ATG codon of Bcl-2 and all of the references teach an oligonucleotide sequence which comprises at least part of SEQ ID NO:1. Since all of the oligonucleotides overlap and all of them have been shown to be effective they are all equivalent and one of ordinary skill in the art would reasonably expect that any antisense oligonucleotide which comprises SEQ ID NO:1 or at least 8 nucleotides of SEQ ID NO:1 would work to lower Bcl-2 expression.

Applicants again argue that Tari *et al.* has been incorrectly characterized since Tari *et al.* teaches that the advantageous properties of liposomes are common to all liposome constructs and that charged lipids have the advantage of high oligonucleotide uptake. Thus, one of ordinary skill in the art would not be motivated to select only neutral lipids based on the teachings of Tari *et al.*

This argument has been fully considered but is not deemed to be persuasive. As discussed above, a fair reading of Tari *et al.* would clearly lead one of ordinary skill in the art to use DOPC as the lipid of choice as Tari *et al.* teaches that DOPC is the preferred embodiment and is one of the easiest lipid to handle, DOPC was the only lipid tested for effectiveness in delivering oligonucleotides to a cell and a comparison of DOPC and DOPS in oligonucleotide uptake efficiency showed the two lipids to be essentially equivalent. Thus, Tari *et al.* provides ample motivation to use DOPC-based liposomes for the delivery of antisense oligonucleotides.

Conclusion

Claims 1-41, 43-50 and 52-56 are rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Schwartzman whose telephone number is (703) 308-7307. The examiner can normally be reached on Monday through Friday from 6:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, George Elliott, can be reached at (703) 308-4003. The fax number for this group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703)-308-0196.

July 15, 1999

ROBERT A. SCHWARTZMAN
PATENT EXAMINER